NTP
National Toxicology Program

Research Concept: Dimethylamine Borane

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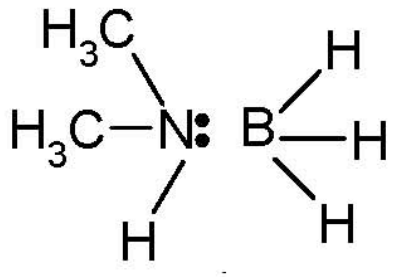
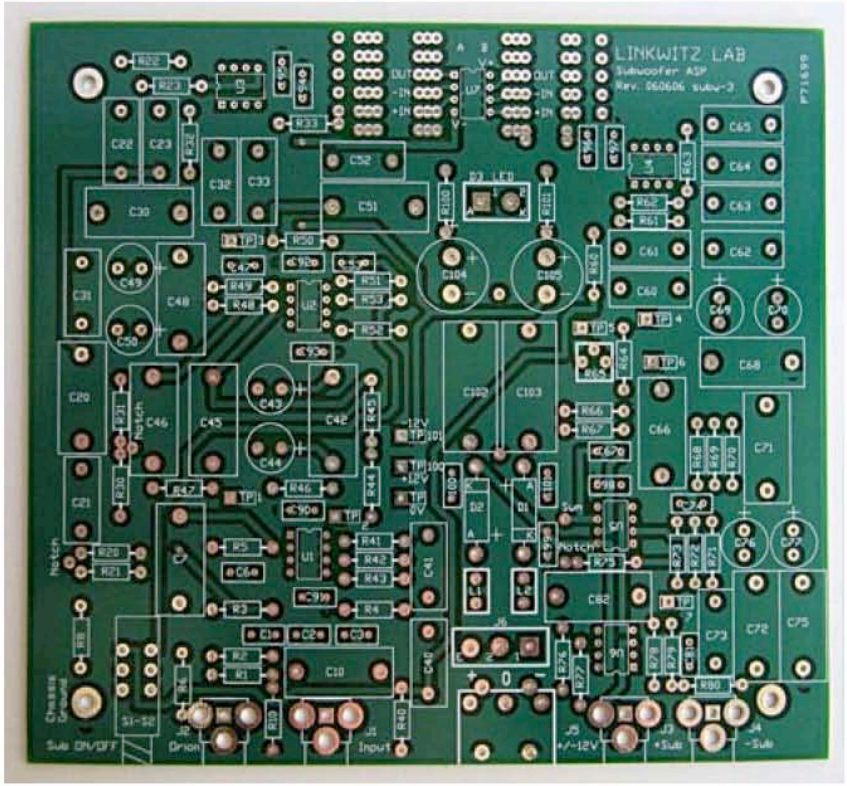
Nomination Background and Rationale

- Nominated by the NIOSH
  - Dermatology cross-sector program
  - Dermal absorption, toxicity and skin sensitization
- Nomination was based on
  - Lack of data
  - Indication of systemic toxicity following accidental exposure



Use and Exposure

- DMAB is a reducing agent widely used in the manufacturing of high-temperature printed electronic circuit boards, thin metal film, semiconductors and power transistors
  - Used in the reduction of aldehydes and ketones to alcohols
  - Used in the electrodeless deposition of metals
- Human exposure is primarily occupational

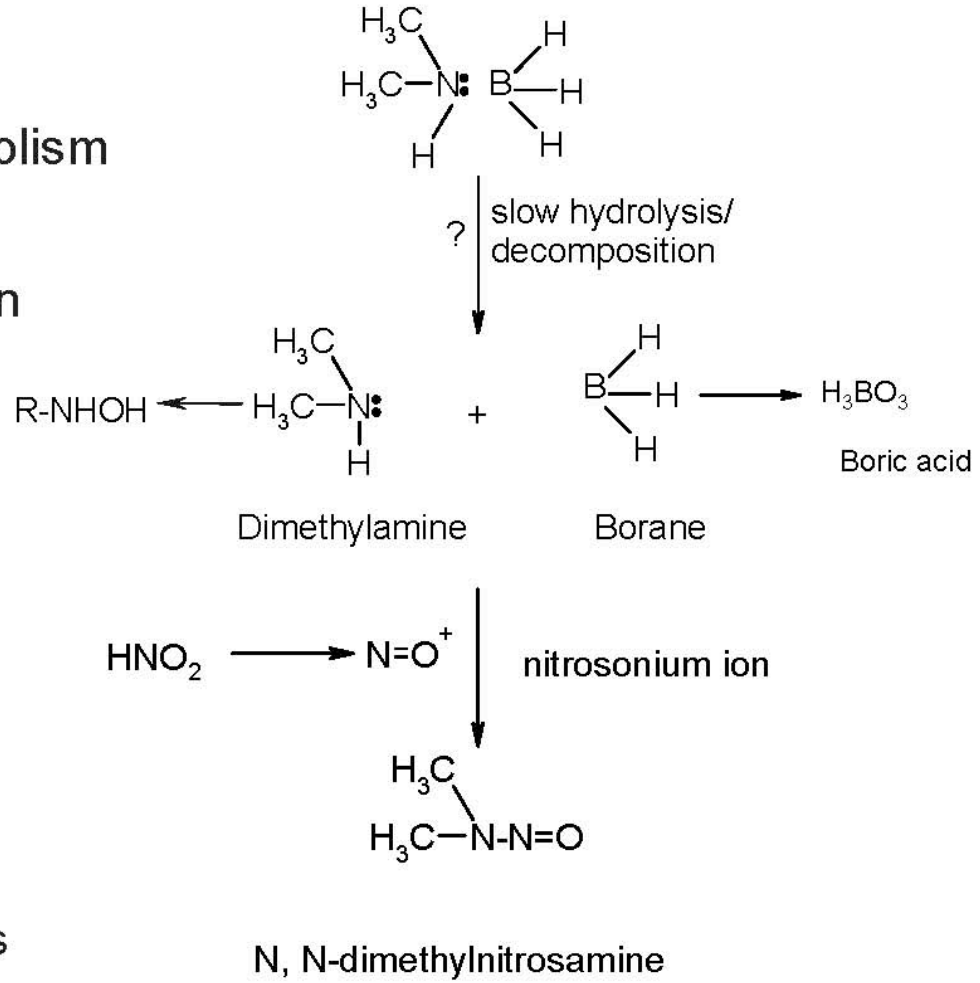


DMAB - Toxicity Studies

- Accidental human exposure
  - Four workers exposed to DMAB in liquid form when a filter was improperly placed in a pipe.
    - Three decontaminated immediately and experienced dizziness, nausea, vomiting, and gastrointestinal issues which resolved in ~24 hrs
    - One individual did not decontaminate immediately and experienced severe and persistent neurologic symptoms
- Acute toxicity (LD_{50}) data for oral, dermal, iv and ip routes of exposure
- No standard repeated-dose subchronic, chronic, neurotoxicity or immunotoxicity (hypersensitivity) data available
- Identified as an irritant on BASF Material Data Safety Sheet (MSDS)
  - No studies available

Toxicokinetics

- No studies were available
- Using METEOR to predict the metabolism of this compound was unsuccessful
- Slow dissociation would likely result in decomposition products
  - Borane
  - Hydrogen borides
  - Dimethylamine
- Potential for formation of dimethylnitrosamine
  - Known carcinogen
  - In the presence of nitrosylating agents



Proposed Research Program

- Hypothesized that DMAB is absorbed via the skin and will target the nervous system and possibly other organ systems
  - Based on the case studies following accidental exposures
- The following specific aims will address this hypothesis and the NIOSH nomination
  - Specific Aim 1 - Evaluate the absorption, distribution, metabolism and excretion of DMAB
    - Does the compound form dimethylamine or dimethylnitrosamine in vivo?
    - Are there amine borane complexes that may cause unique toxicity?

Proposed Absorption, Distribution, Metabolism and Excretion studies for DMAB

- Dermal absorption, penetration and metabolism in human skin in vitro
- ADME in male rats following dermal administration
- ADME in male rats following iv administration
  - Estimate of bioavailability from dermal and oral routes of exposure
- ADME in male rats following oral gavage
  - Effect of dose and route on ADME
  - Acidity of the stomach and nitrosylating agents in the GI tract suggest that dimethylnitrosoamines may form with this route of exposure

Proposed Research Program (continued)

- Specific Aim 2 - Evaluate the genotoxicity of DMAB
  - These studies will be conducted in parallel to the ADME studies
- Specific Aim 3 - Evaluate the potential for DMAB to induce dermal irritancy and hypersensitivity
  - These studies will be conducted in parallel to the ADME studies
- Specific Aim 4 - Based on the data obtained in these studies, the need to conduct standard repeat-dose toxicology studies will be evaluated
  - If warranted, conduct 14- and 90-day toxicology studies via the dermal route of exposure
  - Neurotoxicity would initially be addressed as part of the 90-day studies

Significance and Expected Outcomes

- Available data are inadequate to evaluate the potential toxicity of DMAB following dermal exposure
- Current exposure limits for this compound are based on dimethylamine and may not take into account toxicity associated with the borane moiety
- These data will be used to determine whether regulatory limits specific for DMAB are needed

Update

- Hypersensitivity studies are in progress
- ADME study design presented to the toxicokinetics faculty in October 2008